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14. ABSTRACT The purpose of this award is to define chemokine receptor signatures that contribute to lymphocyte trafficking into target organs in human graft-versus-host disease (GHVD). We use T-cell receptor deep sequencing to characterize the repertoire of effector T-cells in allogeneic hematopoietic stem-cell transplant (HSCT) recipients and identify the role of chemokine receptors in effector cell infiltration of target organs. In the recent funding period we studied blood and tissue samples from several allogeneic HSCT recipients and found that the clonal repertoire of CCR5+ T-cells was distinct from CCR5- T-cells, implying that CCR5 is a close-specific marker and not a general activation marker. We further characterized the clonal diversity and found that the asymmetry in clonal diversity of CCR5+ and CCR5- T-cells is characterized by specific Vgene usage. We are currently verifying this finding in additional patients and characterizing the presence CCR5+ clones in target organs of GVHD.					
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Introduction

The purpose of this study is to use genomic techniques to characterize effector T-cells that govern immune responses after allogeneic hematopoietic stem-cell transplantation (HSCT) in humans. Control of donor T-cells recruitment into target organs is a potentially effective strategy to reduce graft-versus-host disease (GVHD) after allogeneic HSCT without compromising the graft-versus-leukemia (GVL) effect. Using deep sequencing of the T-cell receptor beta chain (TCRB), we aim to identify the clonal diversity of T-cells after allogeneic HSCT and uncover the role of specific chemokine receptors in the trafficking of effector T-cells that are responsible for the GVH and GVL responses.

Keywords

Chemokine receptor

Chemokine

CCR5

Graft-versus-host disease

Allogeneic stem-cell transplantation

Overall Project Summary

Task 1. Regulatory

We completed regulatory submission and received IRB approval of a protocol named “Study of the graft-versus-host and graft-versus-tumor responses after allogeneic stem-cell transplantation”. This protocol provides access to tissue biopsies and bone marrow biopsies from patients who underwent allogeneic HSCT at the University of Pennsylvania in the past 15 years.

Task 2. Specimen Selection and Clinical Database

A full time research coordinator, Lisa Crisalli, was hired for my lab for the purpose of coordinating biospecimen banking, annotating their information, and selecting appropriate specimens for this and other projects. We have completed the identification of appropriate patient samples for Aim 1 and Aim 2 using specific criteria, primarily pertaining to the availability of tissue biopsies with sufficient quantity from at least one GVHD organ in tandem with a peripheral blood mononuclear cell (PBMC) sample that was cryo-preserved. Details about sample availability for Aim 1 and Aim 2 are displayed in Table 1. During the 2nd year of the award we have increased the number of eligible patients for Aim 2 due to the rapid accrual to our phase II study using the CCR5 antagonist maraviroc for GVHD prevention (<http://clinicaltrials.gov/show/NCT01785810>). This trial has completed 90% of patient accrual ahead of schedule and preliminary findings were presented At ASH 2014 (Reshef et al. Extended CCR5 Blockade in Graft-Versus-Host Disease Prophylaxis - a Phase II Study, ASH 2014).

Table 1. Identification of appropriate biospecimens.

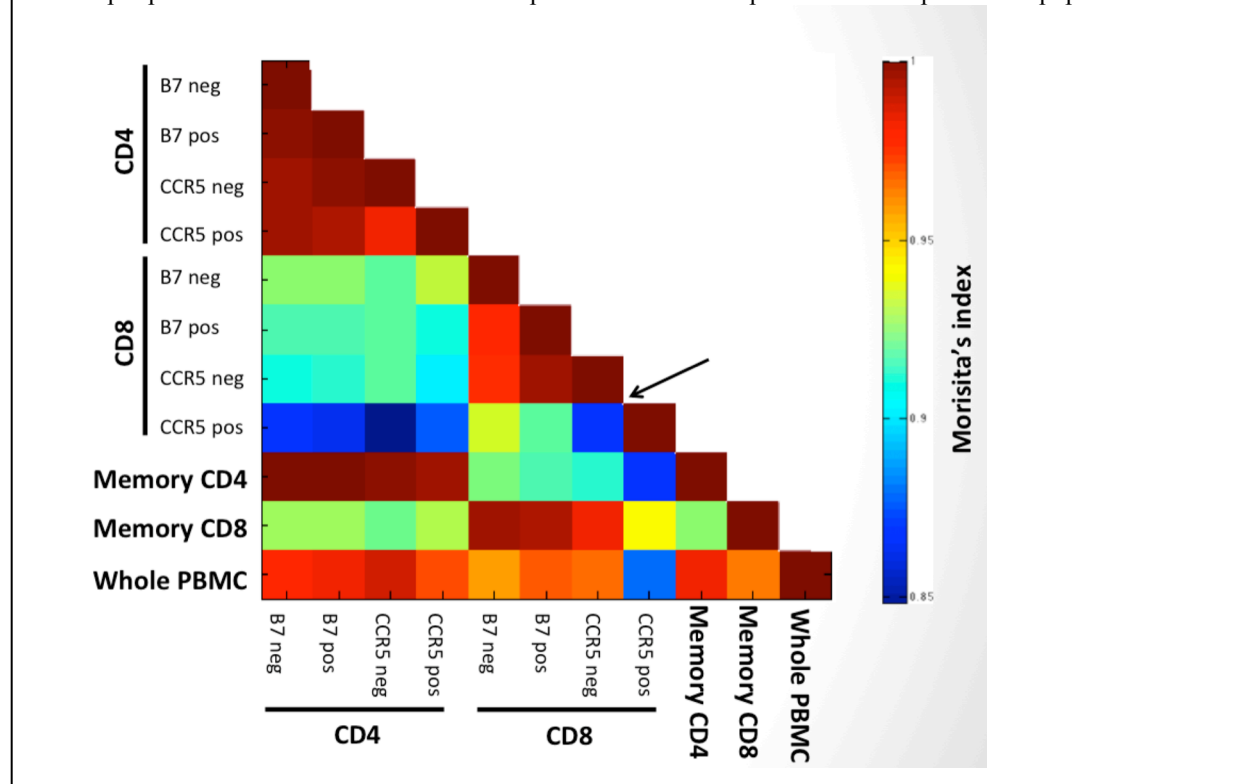
Aim	Patient cohort	PBMC + GVHD biopsy from 1 organ	PBMC + GVHD biopsy from 2 organs	PBMC + GVHD biopsy from 3 organs
Aim 1	Myeloablative HSCT	13	8	5
	Reduced-intensity HSCT	20	8	4
Aim 2	Patients treated with maraviroc on a clinical trial	10	4	2

Task 3-4. Determine the role of chemokine receptor expression in regulating the organ distribution of effector T-cells after allogeneic stem-cell transplantation (Aim 1).

To characterize the clonal diversity that correlates with specific chemokine receptor expression, we initially performed deep sequencing of TCRB on a PBMC sample from a patient 60 days following allogeneic HSCT. TCRB sequencing was conducted on whole PBMC and then on flow-sorted populations of memory CD4 and CD8 T-cells, CCR5-positive, CCR5-negative, integrin β 7-positive and integrin β 7-negative memory T-cells. We then compared the clonal repertoire of each subpopulation using Morisita's Index, a statistical test that measures the overlap between diverse populations (Figure 1). A high Morisita index indicates significant similarity between populations and a low index indicates a great distance between populations. As expected, CD4 clones were different from CD8 clones and they were both similar to their

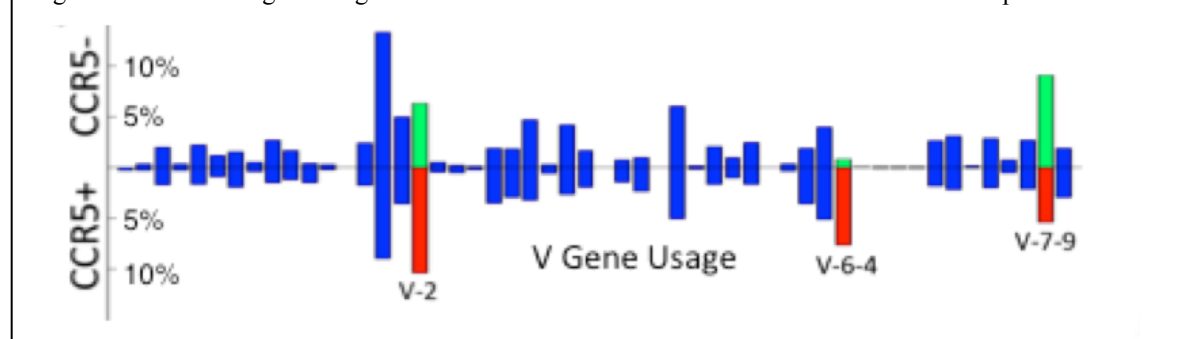
parent population. However, CCR5+ and CCR5- clones had significantly less overlap within the CD8 compartment compared to the CD4 compartment (see arrow in Figure 1). In contrast, integrin $\beta 7$ -positive clones were still similar to integrin $\beta 7$ -negative clones in both the CD4 and CD8 compartments.

Figure 1. The repertoire of CD8⁺CCR5⁺ cells is uniquely biased. TCRB sequencing of flow-sorted T-cell populations demonstrate differences in the clonal diversity of CD8⁺ T-cell based on CCR5 expression. The heatmap represents the Morisita Index for comparison of the overlap between each paired cell populations.

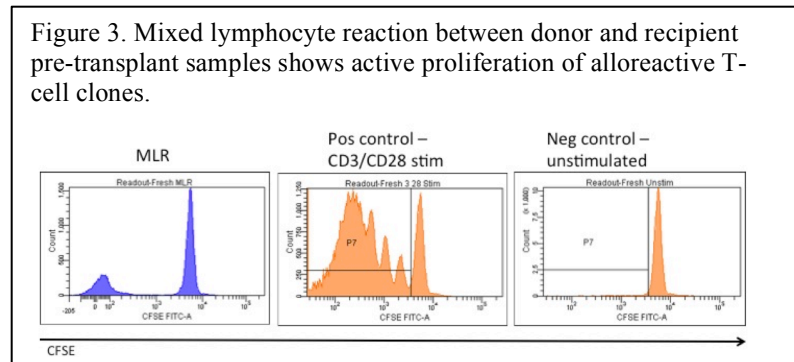


We then analyzed the V region gene usage of T-cell clones in each population in order to identify the source for the bias in clonal diversity within the CD8⁺ cell population. We compared the frequency of V gene usage in CCR5⁺ and CCR5⁻ T-cell populations within the memory CD8 cell compartment (Figure 2). We found that the bias was driven by asymmetry in the usage of 3 V genes (V-2, V-6-4 and V-7-9). We have reproduced this finding in additional allogeneic HSCT recipients and demonstrated a clonal bias in all of them, although the V genes that had differential usage were not the same in all transplanted patients. These findings suggest that CCR5 expression on CD8 cells is not driven solely by global activation status of T-cells, but is a clonal phenomenon that is likely related to certain antigen-specificities.

Figure 2. A bias in V gene usage is identified in CD8⁺ CD45R⁺ T-cells based on CCR5 expression.

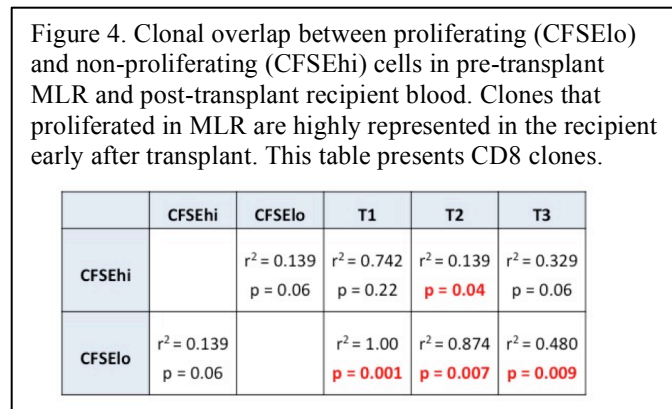


We then hypothesized that CCR5 expression is specific to alloreactive T-cell clones. To this end, we developed a platform to isolate alloreactive T-cell clones by conducting a mixed lymphocyte reaction using pre-transplant donor and recipient samples. We cultured donor and irradiated recipient PBMC at a ratio of 5:1 for 5 days after staining with carboxyfluorescein succinimidyl ester (CFSE) and then flow-sorted proliferating cells (CFSEdim) and non-proliferating cells (Figure 3). In addition, we flow-sorted CD45RO+ cells from 3 time points (t1, t2, t3) post-transplant, extracted DNA and performed TCR sequencing on all samples.



We found that clonal diversity increased with time post-transplant. At t1, the 25 most frequent clones represented 68% of all reads, but at later time points, the 25 most frequent clones only composed 46% and 41% of the total reads at t2 and t3 respectively, reflecting an increase in clonal diversity with time.

We then examined whether TCRB sequencing adequately identifies and tracks alloreactive T-cell clones in vivo. By sequencing the pre-transplant MLR CFSElo and CFSEhi cell populations and comparing them to post-transplant recipient samples at 3 time points, we found that there was high clonal overlap between pre-transplant MLR and post-transplant recipient samples, with CFSElo T-cell clones having much higher overlap than CFSEhi clones (Figure 4). The degree of overlap also decreased with time after transplant, as expected due to clonal expansion, an increase in diversity and formation of new thymic-derived clones.



We then flow-sorted post-transplant samples into CCR5⁺ and CCR5⁻ cell populations and performed TCRB sequencing to demonstrate the enrichment of alloreactive T-cells with CCR5 positivity. These results are currently being analyzed. In addition, we await the sequencing results of 3 more donor-recipient MLRs to validate these findings.

Task 5-6. Determine the effect of targeted chemokine receptor blockade on trafficking patterns of T-cell clones (Aim 2).

We continue to make progress in biospecimen collection for Aim 2. So far 34 patients were enrolled and treated on this clinical trial, which opened in April 2013. We anticipate completion of accrual of 37 patients by August 2015. Extensive biospecimen collection was built into this clinical protocol, including collection of fresh biopsy material from patients who experience

symptoms of GVHD. So far 11 biopsies were collected and analyzed by flow cytometry. TCRB sequencing will be conducted as part of the next steps of this project to demonstrate the effect of CCR5 blockade on clonal diversity.

Task 7-8. Data publication and grant submission.

Preliminary data from this research project have been presented at grand rounds at Columbia University Medical Center and Memorial Sloan Kettering Cancer Center. Abstracts that summarize data directly related to this proposal were presented at the ASH Annual Meeting in December 2014 and the Meeting of the American Society of Blood and Marrow Transplantation in February 2015. We anticipate that data will mature into peer-reviewed publications and within the next year.

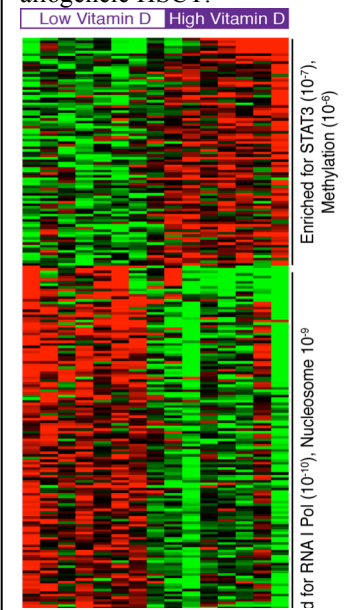
Additional Directions

Through this career development award, my lab developed expertise in analyzing human T-cells from allogeneic HSCT recipients using genomic approaches. This has been greatly facilitated by the close collaboration with the lab of Dana Pe'er at Columbia University that is fostered by this award. As a result, our study of patient samples in this project has led to an unexpected result; we found that the chemokine receptor expression (CCR5 in particular) closely correlated with vitamin D levels (Ganetsky et al. Vitamin D Deficiency Predicts Acute Cutaneous Graft-Versus-Host Disease in Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation. 2014 Tandem Meetings). We then investigated the mechanism underlying the effect of vitamin D levels on T-cell function by conducting functional assays and gene expression profiling of day-30 T-cells from allogeneic HSCT recipients. By conducting gene expression profiling, we demonstrated that low vitamin D levels correlated with overexpression of histones, reflecting a high proliferative state in T-cells, a finding, which we then validated in T-cell proliferation assays. We also found that STAT3 activation was closely related to vitamin D levels, a finding that may explain higher rates of acute GVHD in patients with low vitamin D, as a result of increased differentiation of Th17 cells when STAT3 is activated. These studies demonstrate a unique ability to infer mechanism by studying whole transcriptome in circulating T-cells from transplant patients, a modality that is critical for the design of translational studies. A manuscript describing these findings is currently in preparation.

Key Research Accomplishments

- Demonstration of differences in T-cell clonal diversity according to CCR5 expression, implying that the expression of CCR5 is linked to specific clones and not to global T-cell activation.
- Identification of specific V region genes in the TCRB gene that are biased towards CCR5 expression.
- Development of a platform that identifies alloreactive clones by MLR and tracks these clones in the recipient post-transplant.

Figure 5. Gene expression profiling reveals differences in proliferation, methylation and STAT3 pathway activation between patients with high and low vitamin D levels on day-30 after allogeneic HSCT.



- Implementation of whole transcriptome gene expression studies in the analysis of post-transplant immune responses in humans.

Conclusion

This study so far demonstrated that following allogeneic stem-cell transplantation, CCR5 expression on donor T-cells might be clonal, leading to a bias in clonal distribution and Vgene usage when comparing CCR5+ and CCR5- T-cell populations. This effect is seen in effector CD8 T-cells but not in effector CD4 T-cells. To enrich our analysis for alloreactive T-cell clones, we added a step that includes an MLR reaction between donor and recipient cells and have demonstrated that this step improves our ability to detect the clones that expand post-transplant in the recipient. The next phase of this project is to identify whether CCR5-positivity is related to organ-specific trafficking and whether blocking CCR5 with a specific antagonist alters the clonal diversity of T-cells that infiltrate specific organs. Work to accomplish these goals is ongoing.

Publications, Abstracts and Presentations

1. Ganetsky A, Richman LP, Frey NV, Vonderheide RH, Porter DL, Reshef R: Vitamin D Deficiency Predicts Acute Cutaneous Graft-Versus-Host Disease in Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant February 2014 Notes: Poster Presentation at the 2014 BMT Tandem Meetings, Dallas, TX
2. Reshef R, Mangan JK, Luger SM, Loren AW, Hexner EO, Frey NV, Stadtmauer EA, Blauser RE, Richman LP, Huffman AP, Ganetsky A, Acosta EP, Hoxie JA, Mick R, Vonderheide RH, Porter DL: Extended CCR5 Blockade in Graft-Versus-Host Disease Prophylaxis - a Phase II Study. Blood December 2014 Notes: Poster Presentation at the 56th ASH Annual Meeting, San Francisco, CA

Inventions, Patents and Licenses

Nothing to report.

Reportable Outcomes

Nothing to report.

Other Achievements

Training and Professional Development

My goal during this award is to develop the knowledge and skills necessary to succeed as an independent physician-scientist. The focus of my work as a new investigator is modulation of cell trafficking to improve the outcomes of allogeneic HSCT, a logical extension to my past work that focused on GVHD. The following activities took place during the 1st year of the award:

Additional projects, collaborations and publications. Preclinical studies revolving around GVHD were initiated with strong collaborators - Taku Kambayashi and Yi Zhang, both R01-funded investigators with expertise in GvHD models. Several clinical collaborations were established with investigators at the University of Michigan (John Levine), Mount Sinai School of Medicine (James Ferrara) and the Working Committees of the Center for international Blood and Marrow Transplant Registry. During the 2nd year of the award these collaborations and projects have matured into the following manuscripts, which include a high-impact paper in JCO (No. 9):

1. Levine JE, Hogan WJ, Harris AC, Litzow MR, Efebra YA, Devine SM, **Reshef R**, Ferrara JLM (2014). "Improved accuracy of acute graft-versus-host disease staging among multiple centers" *Best Prac Res Clin Haematol* 27:283-7
2. **Reshef R**, Porter DL (2015). "Reduced-intensity conditioning for allogeneic hematopoietic stem-cell transplantation in adults with acute myeloid leukemia." *Bone Marrow Transplant* 50:759-69
3. Karimi M, Bryson JL, Richman LP, Fesnak AD, Leichner TM, Satake A, Vonderheide RH, Raulet DH, **Reshef R**, Kambayashi T (2015). "NKG2D expression by CD8+ T-cells contributes to GVHD and GVT effects in a murine model of allogeneic HSCT" *Blood* 125: 3655-63
4. Ganetsky A, Miano TA, Hughes ME, Vonderheide RH, Porter DL, **Reshef R** (2015). "Lack of a Significant Pharmacokinetic Interaction Between Maraviroc and Tacrolimus in Allogeneic Hematopoietic Stem Cell Transplant Recipients." *J Antimicrob chemother* (In Press)
5. Bagley SJ, Sehgal AR, Frey NV, Gill S, Hexner EO, Loren AW, Mangan JK, Porter DL, Stadtmauer EA, **Reshef R**, Luger SM (2015). "Acute Cholecystitis Is a Common Complication Following Allogeneic SCT and Is Associated With Use of Total Parenteral Nutrition" *Biol Blood Marrow Transplant* 21: 768-71
6. Goyal SD, Zhang MJ, Wang HL, Akpek G, Copelan EA, Freytes C, Gale RP, Hamadani M, Inamoto Y, Kamble RT, Lazarus HM, Marks DI, Nishihori T, Olsson RF, **Reshef R**, Ritchie DS, Saber W, Savani BN, Seber A, Shea TC, Tallman MS, Wirk B, Bunjes DW, Devine SM, de Lima M, Weisdorf DJ, Uy GL (2015). "Allogeneic Hematopoietic Cell Transplant for Acute Myeloid Leukemia: No Impact of Pre-transplant Extramedullary Disease on Outcome" *Bone Marrow Transplant* (In Press)
7. Urbano Ispizua A, Pavletic S, Flowers ME, Klein JP, Zhang M, Carreras J, Montoto S, Perales MA, Aljurf MD, Akpek G, Bredeson C, Costa L, Dandoy C, Freytes C, Fung H, Peter R, Gibson J, Hamadani M, Hayashi RJ, Inamoto Y, Inwards DJ, Lazarus HM, Maloney DG, Martino R, Munker R, Nishihori T, Olsson R, Rizzieri DA, **Reshef R**, Saad A, Savani BN, Schouten HC, Smith S, Socie G, Wirk B, Yu L, Saber W (2015). "The Impact Of Graft versus Host Disease On Relapse Rate In Patients With Lymphoma Depends On The Histological Sub-Type And The Intensity Of The Conditioning Regimen" *Biol Blood Marrow Transplant* (In Press)

8. Luskin MR, Heil DS, Tan KS, Choi SM, Stadtmauer EA, Schuster SJ, Porter DL, Vonderheide RH, Bagg A, Heitjan DF, Tsai DE, **Reshef R** (2015). "The Impact of EBV Status on Disease Characteristics and Outcomes of Post-Transplantation Lymphoproliferative Disorder in Adult Solid Organ Transplant Recipients" *Am J Transplant* (In Press)
9. **Reshef R**, Huffman AP, Gao A, Luskin MR, Hexner EO, Loren AW, Frey NV, Stadtmauer EA, Luger SM, Mangan JK, Nasta SD, Gill SI, Sell M, Kambayashi T, Richman LP, Vonderheide RH, Mick R, Porter DL (2015). "High Graft CD8 Cell Dose Predicts Improved Survival and Enables Better Donor Selection In Allogeneic Stem-Cell Transplantation With Reduced-Intensity Conditioning" *J Clin Oncol* (In Press)

In addition, the following manuscripts are currently under review:

1. Seftel MD, Neuberg D, Zhang M, Wang H, Akpek G, Bachanova V, Bacher U, Ballen K, Baron F, Bashey A, Bergeron J, Cahn J, Camitta BM, Copelan EA, Couban S, DeAngelo DJ, de Lima M, Deol A, Freytes C, Gale RP, Gergis U, Hamadani M, Hogan WJ, Kebriaei P, Kharfan-Dabaja M, Lazarus HM, Litzow MR, Loren AW, Miller A, Nishihori T, Norkin M, Olsson RF, Paulson K, **Reshef R**, Saber W, Sabloff M, Sandmaier B, Sallan SE, Savani BN, Schouten H, Tallman MS, Vij R, Woolfrey A, Wiernik PH, Wirk B, Wood WA, Weisdorf DJ. "Pediatric-Inspired Therapy Versus Allografting for Philadelphia Chromosome Negative Adult ALL in First Complete Remission." (Under Review)
2. Mochizuki K, Meng L, Mochizuki I, Tong Q, He S, Liu Y, Purushe J, Fung H, Zaidi RM, **Reshef R**, Blazar BR, Yagita H, Mineishi S, Zhang Y. "Programming of Donor T Cells Using Allogeneic DLL4-positive Dendritic Cells to Reduce GvHD in Mice." (Under Review)
3. Meng L, Bai Z, He S, Mochizuki K, Liu Y, Purushe J, Sun H, Wang J, Yagita H, Mineishi S, Fung H, Yanik GA, Caricchio R, Fan X, Crisalli LM, **Reshef R**, Zhang Y, and Zhang Y. "Human circulating dendritic cells require the Notch ligand DLL4 to induce Th1 and Th17 differentiation." (Under Review)

Grant Development. The following grant applications were submitted during this award period:

1. "The role of surface NKG2D expression by NK cells in the graft-versus-leukemia response" (Reshef, Kambayashi Co-PIs) – Hematologic Malignancies Translational Center of Excellence Pilot Project. **Funded.**
2. "Preclinical evaluation of CCR2/CCR5 blockade to increase efficacy and reduce toxicity of PD-1/CTLA-4 inhibition for melanoma" (Reshef, Garfall Co-PIs) – Institute for Immunology pilot grant. **Not Funded.**
3. "Preclinical evaluation of CCR2/CCR5 blockade to increase efficacy and reduce toxicity of PD-1/CTLA-4 inhibition for melanoma" (Reshef, Garfall Co-PIs) – Penn/Wistar NCI SPORE pilot grant. **Funded.**
4. "EZH2-mediated epigenetic effects and alloimmunity" (PI – Zhang. Reshef, Co-Investigator) – NIH R01. **Resubmission under review.**
5. "Blockade of lymphocyte trafficking as a novel therapeutic target in allogeneic stem-cell transplantation" (Reshef PI) – Damon Runyon Clinical Investigator Award. **Not Funded.**

Training in tumor and transplant immunology. During the award period I continued to be a member of Dr. Robert Vonderheide's laboratory with increasing independence. During the 2nd year of the award I hired a technician and a post-doctoral fellow. Dr. Vonderheide and I met weekly to review data, to discuss ongoing experiments and for didactic sessions. I participated in weekly meetings and other scientific activities by the Translational Research Program (TRP), led by Carl June, an internationally recognized leader in translational immunology.

Research conferences and meetings. In the past year I attended and presented abstracts at the Annual Meeting of the American Society of Clinical Oncology, the Annual Meeting of the American Society of Hematology and the meeting of the American Society of Blood and Marrow Transplantation. In addition I presented in meetings on Penn campus.

Leadership roles. The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) has appointed me as co-chair of a multi-institutional trial that tests novel strategies in GvHD prevention (BMT-CTN 1203). During the 2nd year of the award this multi-center clinical trial, which builds on findings directly related to this DOD project, opened for accrual in 30 sites in the US and is currently enrolling patients ahead of schedule with more than a third of accrual already completed. My leadership position as a co-chair of the study allows me to take a leading role in the international community of HSCT and GVHD experts. The current DOD project will inform the design of follow up clinical studies and will help design the correlative studies that are an essential part of this multicenter trial. During the 2nd award year, I expanded my leadership role with the BMT-CTN by becoming the local PI of 2 additional clinical trials within the network – BMT-CTN 0903 that aims to assess the feasibility of allogeneic HSCT in patients with HIV, and BMT-CTN 1301 which tests novel strategies for GVHD prevention in the myeloablative setting. These projects provide me with experience in global collaborative research.

Career Development Plan for Columbia University

On July 1st, 2015 I will commence my position at Columbia University Medical Center as the Director of Translational Research for the Blood and Marrow Transplantation Program. I will be appointed a Principal Investigator in the Columbia Center for Translational Immunology (CCTI) under the leadership of Megan Sykes, M.D., a renowned scientist in transplantation immunology.

As part of my position at Columbia University, I was offered the following resources, which are critical for the continued success of this career development award:

- Lab space in the CCTI to accommodate the work of 3 scientists and a lab manager.
- Access to core resources that are unique to CCTI members, including a flow cytometry core, humanized mice core, large animal facility, microscopy.
- Grant management, IT support and facilities management of the CCTI.
- An office in the CCTI, adjacent to the lab.
- Clinical research and regulatory support from the Clinical Protocol and Data Management (CPDM) Office at Columbia University Medical Center.
- Clinical work will be conducted as part of the new BMT group at Columbia, under the leadership of Markus Mapara, MD. The BMT group includes 4 physicians with a strong research orientation. Transplants are performed in a new inpatient unit that was completely renovated with state-of-the-art equipment and inaugurated 2 years ago. The new unit is located at the Harkness Pavilion with a bridge connecting to the Black Building where the CCTI is located. The BMT program is certified by the Foundation for the Accreditation of Cellular Therapy (FACT) and the National Marrow Donor Program (NMDP) and is working closely with the leukemia, lymphoma and myeloma groups at Columbia to ensure patients' access to transplant resources.
- Protected time is guaranteed to ensure the completion of this award.

My mentor at Columbia University will be Megan Sykes, director of the CCTI and a leader in the field of transplantation research. She has expertise in areas directly related to this proposal and has published recently on the use of TCRB sequencing for the assessment of transplant immune responses (Morris et al. *Sci Trans Med* 2015). I anticipate that all career development activities will continue uninterrupted with the move to Columbia.

References

None

Appendices

None